

Biomarker discovery in heart failure

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Summary

Heart failure (HF) occurs when the heart muscle does not pump sufficient blood to fulfill the requirements of the body as it should. HF is one of the most important causes of hospitalization for patients aged 65 and over, which increasingly imposes high health care costs related to relatively long hospital stays. HF is a very complex disease and it is difficult to diagnose and monitor the progression of the disease based on clinical signs and symptoms only. This is even more difficult for elderly patients with multiple comorbidities. Therefore, biomarkers (circulating markers that can be measured in the blood) that reflect one or several pathways might be useful as diagnostic or prognostic factors in HF. Biomarkers may also have therapeutic implications for individualized therapy. Guiding HF therapy by a single biomarker, measured only at one time point, is limited because one biomarker at one time point cannot cover the extensive pathophysiological pathways involved in HF. Performing repeated measurements of several biomarkers, however, may lead towards precision in medical therapy in HF patients.

This thesis had two main objectives; namely a medical objective and a methodological one. The medical objective of this thesis was to investigate the predictive value of biomarkers to predict the response to therapy in the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) study. The methodological objective of the thesis was to develop new methods with the aim to be used for addressing the medical objective and to facilitate investigation of biomarkers.

In Chapter 2, we provided general background information about the TIME-CHF study and the statistical methods applied in this thesis.

In Chapter 3, we employed the Prentice, Williams and Peterson Gap-Times model [10, 106] to investigate the effect of N-terminal pro-B-type Natriuretic Peptide (NT-proBNP)-guided therapy on the recurrence of all-cause hospitalization events (all-cause hospitalization or death) and HF hospitalization events (HF hospitalization or death) in the TIME-CHF study. We observed that the NT-proBNP-guided therapy as compared to standard therapy did not reduce the risk of first all-cause hospitalization event. However, we showed that NT-proBNP-guided therapy has a beneficial effect on the second and third all-cause hospitalization events, indicating that considering repeated events may be meaningful in interventional clinical trials. When considering pre-stratified age groups, these effects were only seen in patients aged <75 years, but not in patients aged ≥ 75 years. In addition, NT-proBNP-guided therapy reduced the risk of first and second HF hospitalization again predominantly in patients aged <75 years.

In this thesis we aimed to move towards developing a biomarker-guided treatment

algorithm for personalized medical HFrEF (HF with reduced Ejection Fraction) therapy (Chapter 6). As a purely hypothesis generating study, we investigated the interaction between multiple repeatedly measured biomarkers and the response to the four most important classes of HF medication regarding the risk of HF hospitalization or death in patients with reduced ejection fraction. For these analyses, we employed logistic Generalized Estimating Equations (logistic-GEE) model [73, 147].

The four HF medications in this study were β -blockers, Renin-Angiotensin System (RAS) blockers, Spironolactone and Loop diuretics. The study also included the following biomarkers: Soluble FMS-Like Tyrosine kinase-1 (SFLT), Growth Differentiation Factor 15, Cystatin-C (CysC), Ferritin, Interleukin-6 (IL6), Placental Like Growth Factor, Sex Hormone-Binding Globulin, Soluble Transferrin Receptor, High Sensitivity Troponin T, Type-1 Procollagen N-terminal Peptide, Uric acid, Blood Urea Nitrogen (BUN), Soluble ST2 (SST2), NT-proBNP, Creatinine, High Sensitivity C-Reactive Protein (HSCRP), Prealbumin (PREA), Osteopontin, Mimican, and Insulin-like Growth Factor-Binding Protein 7.

The results showed that loop diuretics up-titration has a beneficial effect for patients with high IL6 or high HSCRP, whereas the opposite was true with low IL6 or low HSCRP. Higher dosage of loop diuretics was associated with poor outcome in patients with high BUN or PREA, but not in those with low levels of these biomarkers. Spironolactone up-titration was associated with lower risk of HF hospitalization or death in patients with high CysC. Patients with a high SFLT concentration may have a worse outcome with higher doses of β -blockers as compared to those on lower doses. Patients with low SFLT levels had a more favourable outcome overall, largely irrespective of β -blockers dose in our population. No treatment biomarker interactions were found for RAS blockers. Such interactions between biomarkers and treatment might help to personalize treatment in HFrEF patients, but prospective validation is required before this approach can be applied to clinical practice. In order to support and assess the accuracy of these results, in Chapter 5, we proposed a new performance measure for logistic-GEE models, which we called Generalized Ranking Accuracy (GRA).

GRA is defined as the probability that a randomly selected instance with positive outcome is ranked higher than a randomly selected instance with negative outcome from another cluster, with logistic-GEE model. There are several advantages with GRA compared with other standard goodness-of-fit criteria for logistic-GEE models: (a) there is no restriction in computation of GRA regarding the number and types of covariates in the model; (b) GRA as a probability is easy to interpret; (c) GRA has an absolute range and can be used for comparing the goodness-of-fit of different logistic-GEE models for different data sets; and (d) by using cross-validation, GRA-CV can be used as a predictive performance criterion for logistic-GEE models. In addition we showed experimentally that GRA is not biased in the presence of two-class imbalanced data. Moreover, we showed

that GRA-CV performs well as a model selection criterion for logistic-GEE models. We note that GRA is also applicable to any model for bipartite ranking trained on clustered data.

Dichotomizing the biomarkers (or any continuous covariates) may make it easier to interpret the obtained statistical results and may help to have a more precise treatment decision. Therefore, we introduced a Bayesian approach (Chapter 4) to estimate cutpoints for continuous covariates. The proposed approach is based on the assumption that the dichotomized covariates are related to an outcome variable through linear regression. In the multivariate setting, this approach can be used to dichotomize all or a subset of the covariates. To the best of our knowledge the proposed Bayesian approach is the first method that can deal with multivariate dichotomization with respect to modeling a continuous outcome variable. We applied the Bayesian approach to estimate the cutpoints for three markers in the TIME-CHF study, the BMI (Body Mass Index) and two biomarkers: SST2 and Mimecan, with respect to NT-proBNP. We observed that the estimated cutpoints and associations of the dichotomized markers with NT-proBNP were in the same line with the recommended cutpoints and previously observed associations in the other studies.